REC'D 10 MAY 2004
WIPO PCT

Kongeriget Danmark

Patent application No.: PA 2003 00649

Date of filing: 30 April 2003

Applicant: (Name and address)
H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

Title: Aromatic oxyphenyl and Aromatic sulfanylphenyl derivatives

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

23 February 2004

Helle Schackinger Olesen

Helle Schackinger Olesen

PATENT- OG VAREMÆRKESTYRELSEN

Modtaget
30 APR. 2003
PVS

Aromatic oxyphenyl and Aromatic sulfanylphenyl derivatives

The present invention relates to novel compounds which are glycine transporter inhibitors and as such effective in the treatment of disorders in the CNS, such as schizophrenia.

Background of the invention

Glutamic acid is the major excitatory amino acid in the mammalian central nervous system (CNS), and acts through two classes of receptors, the ionotropic and metabotrobic receptors, respectively. The ionotropic glutamate receptors are divided into three subtypes based on the affinities of agonists for these receptors, namely *N*-methyl-D-aspartate (NMDA), (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kainic acid (or kainate) receptors.

The NMDA receptor contains binding sites for modulatory compounds such as glycine and polyamines. Binding of glycine to its receptor enhances the NMDA receptor activation. Such NMDA receptor activation may be beneficial for the treatment of schizophrenia and other diseases linked to NMDA receptor dysfunction. An activation can be achieved by an inhibitor of the glycine transporter.

Molecular cloning has revealed the existence of two types of glycine transporters, GlyT-1 and GlyT-2, wherein GlyT-1 can be further subdivided into GlyT-1a, GlyT-1b and GlyT-1c.

The NMDA receptor is blocked by compounds such as phencyclidine which induce a psychotic state which resembles schizophrenia. Likewise, the NMDA antagonists, such as ketamine, induce negative and cognitive symptoms similar to schizophrenia. This indicates that NMDA receptor dysfunction is involved in the pathophysiology of schizophrenia.

The NMDA receptor has been associated with a number of diseases, such as pain (Yaksh *Pain* **1989**, 37, 111-123), spasticity, myuoclonus and epilepsy (Truong et. al. *Movement Disorders* **1988**, 3, 77-87), learning and memory (Rison et. al. *Neurosci.*

Biobehav. Rev. 1995, 19, 533-552), post-traumatic stress disorder (abbreviated: PTSD) (Heresco-levy et. al. *The International Journal of Neuropsychopharmacology*, 2002, 5:301-307, entitled: "Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder").

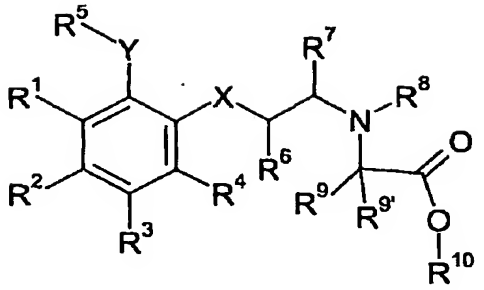
Glycine transporter antagonists or inhibitors are believed to be highly beneficial in the treatment of schizophrenia (Javitt WO 97/20533).

Glycine transport antagonists or inhibitors could be useful for the treatment of both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke. Likewise, convulsive disorders such as epilepsy, spasticity or myoclonus may benefit from glycine transporter antagonists.

Clinical trials with glycine have been reported, Javitt et. al. *Am. J. Psychiatry* 1994, 151, 1234-1236 and Leiderman et. al. *Biol. Psychiatry* 1996, 39, 213-215. The treatment with high-dose glycine is reported to improve the symptoms of schizophrenia. There is a need for more efficient compounds for the treatment of NMDA associated diseases.

Summary of the invention

The present invention relates to compounds of formula I which are potent inhibiters of the glycine transport. In one aspect the present invention relates to a compound of the general formula I



wherein the substituents are as defined below.

Furthermore, the invention provides a compound of formula I as above for use as a medicament.

Moreover, the invention provides a pharmaceutical composition comprising a compound of formula I as above or a pharmaceutically acceptable salt thereof, e.g. a pharmaceutically acceptable acid addition salt thereof, and at least one pharmaceutically acceptable carrier or diluent.

The invention also provides the use of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus.

The invention also provides the use of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of post-traumatic stress disorder.

The invention also provides a method for the treatment of diseases selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof.

The invention also provides a method for the treatment of post-traumatic stress disorder in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof.

Definitions

The term "halogen" means fluoro, chloro, bromo or iodo.

The expression "C_{1-6}-alk(en/yn)yl" means a C_{1-6}-alkyl, C_{2-6}-alkenyl or a C_{2-6}-alkynyl group. The expression "C_{3-8}-cycloalk(en)yl" means a C_{3-8}-cycloalkyl- or cycloalkenyl group.

The term "C_{1-6} alkyl" refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

The term "C_{2-6} alkenyl" designate such groups having from two to six carbon atoms, including one double bond, including but not limited to ethenyl, propenyl, and butenyl.

The term "C_{2-6} alkynyl" designate such groups having from two to six carbon atoms, including one triple bond, including but not limited to ethynyl, propynyl and butynyl.

The term "C_{3-8} cycloalkyl" designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term "C_{3-8} cycloalkenyl" designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

In the term "C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl", C_{3-8}-cycloalk(en)yl and C_{1-6}-alk(en/yn)yl are as defined above.

The terms "C_{1-6}-alk(en/yn)yloxy", "C_{1-6} alk(en/yn)ylsulfanyl", "hydroxy-C_{1-6}-alk(en/yn)yl", "halo-C_{1-6}-alk(en/yn)yl", "halo-C_{1-6}-alk(en/yn)yloxy", "C_{1-6}-alk(en/yn)ylsulfonyl" etc. designate such groups in which the C_{1-6}-alk(en/yn)yl is as defined above, and "halo" means halogen.

The term "C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl" designate such group in which the C_{1-6} alk(en/yn)ylsulfanyl and C_{1-6}-alk(en/yn)yl are as defined above.

As used herein, the term "C_{1-6}-alk(en/yn)yloxycarbonyl" refers to groups of the formula C_{1-6}-alk(en/yn)yl-O–CO-, wherein C_{1-6}-alk(en/yn)yl are as defined above.

As used herein, the term "acyl" refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group, wherein aryl is defined below.

The term "together with the nitrogen form a saturated 3-7-membered heterocyclic ring" as used herein refers to saturated ring systems having from 2 to 6 carbon atoms and one nitrogen, such as 1-pyrrolidinyl, 1-piperidinyl or 1-azepinyl, all of which may be further substituted with C_{1-6}-alkyl.

The term "together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S, or N" as used herein refers to saturated or unsaturated ring systems having from 2 to 6 carbon atoms and one nitrogen, or 2 to 5 carbon atoms and two nitrogens, one nitrogen and one oxygen, or one nitrogen and one sulphur, such as 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or 1-pyrazolyl, all of which may be further substituted with C_{1-6}-alkyl.

The term "aryl" refers to carbocyclic, aromatic systems, such as phenyl and naphthyl.

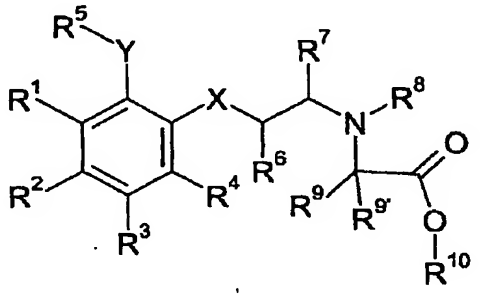
The term "monocyclic heteroaryl" refers to 5- to 6- membered aromatic systems containing 1 to 5 carbon atoms and one or more heteroatoms selected from O, S or N, such as 5-membered monocyclic rings such as oxathiazoles, dioxazoles, dithiazoles, oxadiazoles, thiadiazoles, triazoles, isoxazoles, oxazoles, isothiazoles, thiazoles, imidazoles, pyrazoles, pyrroles, furan(s) or thiophene(s), e.g. 3*H*-1,2,3-oxathiazole, 1,3,2-oxathiazole, 1,3,2-dioxazole, 3*H*-1,2,3-dithiazole, 1,3,2-dithiazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1*H*-1,2,3-triazole, isoxazole, oxazole, isothiazole, thiazole, 1*H*-imidazole, 1*H*-pyrazole, 1*H*-pyrrole, furan or thiophene, or 6-membered monocyclic rings such as oxathiazines, dioxazines, dithiazines, oxadiazines, thiadiazines, triazines, oxazines, thiazines, pyrazines, pyridazines, pyrimidines, oxathiins, dioxins, dithiins, pyridines, pyrans or thiins, e.g. 1,2,3-oxathiazine, 1,2,4-oxathiazine, 1,2,5-oxathiazine, 1,4,2-oxathiazine, 1,4,3-oxathiazine, 1,2,3-dioxazine, 1,2,4-dioxazine, 4*H*-1,3,2-dioxazine, 1,4,2-dioxazine, 2*H*-1,5,2-dioxazine, 1,2,3-dithiazine, 1,2,4-dithiazine, 4*H*-1,3,2-dithiazine, 1,4,2-dithiazine, 2*H*-1,5,2-dithiazine, 2*H*-1,2,3-oxadiazine, 2*H*-1,2,4-oxadiazine, 2*H*-1,2,5-oxadiazine, 2*H*-1,2,6-oxadiazine, 2*H*-1,3,4-oxadiazine, 2*H*-1,2,3-thiadiazine, 2*H*-1,2,4-thiadiazine, 2*H*-1,2,5-thiadiazine, 2*H*-1,2,6-thiadiazine, 2*H*-1,3,4-thiadiazine, 1,2,3-triazine, 1,2,4-triazine, 2*H*-1,2-oxazine, 2*H*-1,3-oxazine, 2*H*-1,4-oxazine, 2*H*-1,2-thiazine, 2*H*-1,3-thiazine, 2*H*-1,4-thiazine, pyrazine, pyridazine, pyrimidine, 4*H*-1,3-oxathiin, 1,4-oxathiin, 4*H*-1,3-dioxin, 1,4-dioxin, 4*H*-1,3-dithiin, 1,4-dithiin, pyridine, 2*H*-pyran or 2*H*-thiin.

The term "alkali metal" refers to lithium, sodium, potassium, and cesium.

Description of the invention

The present invention relates to compounds of formula I which are potent inhibiters of the glycine transporter and consequently they are useful in treating diseases associated with NMDA dysfunction, such as schizophrenia.

In one aspect the present invention relates to a compound of the general formula I



wherein

X is O, S or $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl;

Y is O or S;

R^1, R^2, R^3 and R^4 are independently selected from hydrogen; halogen; cyano; nitro; C_{1-6}-alk(en/yn)yl; C_{1-6}-alk(en/yn)yloxy; C_{1-6}-alk(en/yn)ylsulfanyl; hydroxy; hydroxy-C_{1-6}-alk(en/yn)yl; halo-C_{1-6}-alk(en/yn)yl; halo-C_{1-6}-alk(en/yn)yloxy; C_{3-8}-cycloalk(en)yl; C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; acyl; C_{1-6}-alk(en/yn)yloxycarbonyl; C_{1-6}-alk(en/yn)ylsulfonyl; aryl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl; monocyclic heteroaryl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl; or

$-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^{13} and R^{14} together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S or N;

R^5 is aryl or monocyclic heteroaryl, optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl, C_{1-6}-alk(en/yn)ylsulfonyl, or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^{15} and R^{16} together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S or N;

R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy, or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl;

R^7 and R^8 are independently selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl; or

R^6 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl, or C_{3-8}-cycloalk(en)yl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl, or C_{3-8}-cycloalk(en)yl; or

R^7 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from

C_{1-6}-alk(en/yn)yloxy, or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H, or C_{1-6} alkyl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl; or

R^8 and R^9 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy, or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl, or C_{3-8}-cycloalk(en)yl, and $R^{9'}$ is selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

R^{10} is H, C_{1-6}-alk(en/yn)yl, aryl, aryl-C_{1-6}-alk(en/yn)yl, wherein aryl is optionally substituted with a halogen, CF_3, OCF_3, CN, NO_2 or C_{1-6}-alk(en/yn)yl; or an alkali metal, such as sodium, potassium or lithium;
or a salt thereof, such as a pharmaceutically acceptable salt.

In an embodiment of formula I X is O. In another embodiment of formula I X is S. In a further embodiment X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from C_{1-6} alkyl, such as methyl. In a further embodiment X is CHR^{11}, wherein R^{11} is selected from C_{1-6} alkyl, such as methyl. In a further embodiment X is CH_2.

In a further embodiment of formula I Y is O. In a further embodiment Y is S.

In a further embodiment of formula I R^1 is hydrogen. In a further embodiment R^1 is selected from C_{1-6}-alkyl, such as methyl, ethyl, n-propyl, isopropyl or t-butyl. In a further embodiment R^1 is selected from a halogen, such as Cl, F, Br or I, e.g. Cl. In a further embodiment of formula I R^1 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl. In a further embodiment of formula I R^1 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} together with the nitrogen form a 3-7-membered

heterocyclic ring selected from 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or 1-pyrazolyl, optionally substituted with a C_{1-6}-alkyl. In a further embodiment of formula I R^1 is phenyl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl, such as phenyl substituted with one or two subtituents, typically one, selected from C_{1-6}-alkyl, or C_{1-6}-alkoxy, e.g. methoxy.

In a further embodiment of formula I R^2 is hydrogen. In a further embodiment R^2 is selected from C_{1-6}-alkyl, such as methyl, ethyl, n-propyl, isopropyl or t-butyl. In a further embodiment R^2 is selected from a halogen, such as Cl, F, Br or I, e.g. Cl. In a further embodiment of formula I R^2 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl. In a further embodiment of formula I R^2 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} together with the nitrogen form a 3-7-membered heterocyclic ring selected from 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or 1-pyrazolyl, optionally substituted with a C_{1-6}-alkyl. In a further embodiment of formula I R^2 is phenyl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl, such as phenyl substituted with one or two subtituents, typically one, selected from C_{1-6}-alkyl or C_{1-6}-alkoxy, e.g. methoxy.

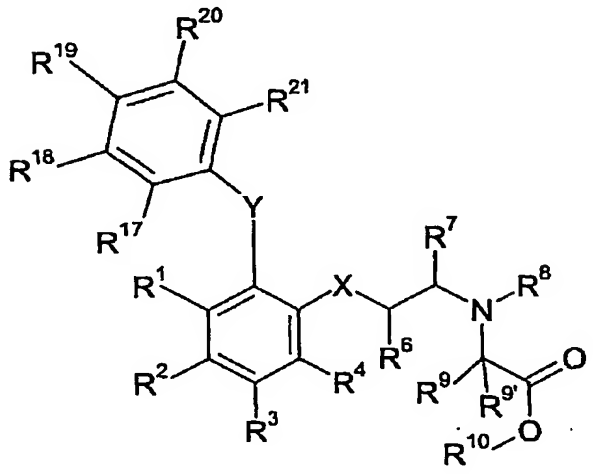
In a further embodiment of formula I R^3 is hydrogen. In a further embodiment R^3 is selected from C_{1-6}-alkyl, such as methyl, ethyl, n-propyl, isopropyl or t-butyl. In a further embodiment R^3 is selected from a halogen, such as Cl, F, Br or I, e.g. Cl. In a further embodiment of formula I R^3 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl. In a further embodiment of formula I R^3 is –

$NR^{13}R^{14}$ wherein R^{13} and R^{14} together with the nitrogen form a 3-7-membered heterocyclic ring selected from 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or 1-pyrazolyl, optionally substituted with a C_{1-6}-alkyl. In a further embodiment of formula I R^3 is phenyl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy,. C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl, such as phenyl substituted with one or two subtituents, typically one, selected from C_{1-6}-alkyl or C_{1-6}-alkoxy, e.g. methoxy.

In a further embodiment of formula I R^4 is hydrogen. In a further embodiment R^4 is selected from C_{1-6}-alkyl, such as methyl, ethyl, n-propyl, isopropyl or t-butyl. In a further embodiment R^4 is selected from a halogen, such as Cl, F, Br or I. In a further embodiment of formula I R^4 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl. In a further embodiment of formula I R^4 is $-NR^{13}R^{14}$ wherein R^{13} and R^{14} together with the nitrogen form a 3-7-membered heterocyclic ring selected from 1-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or 1-pyrazolyl, optionally substituted with a C_{1-6}-alkyl. In a further embodiment of formula I R^4 is phenyl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl, such as phenyl substituted with one or two subtituents, typically one, selected from C_{1-6}-alkyl or C_{1-6}-alkoxy, e.g. methoxy.

In a further embodiment of formula I R^5 is phenyl. In a further embodiment R^5 is phenyl substituted with a halogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. The phenyl ring may contain 1, 2, 3, 4 or 5 substituents, typically 1 or 2 substituents independently selected from the above, such as Cl, F, methyl, t-butyl,

methoxy, methylsulfanyl or CF_3. To illustrate this, without limiting the invention in any way, the following sub-structure of formula I is an embodiment of the invention:



(Ia)

wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, X and Y are as defined in formula I above, including the described embodiments above and below, and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are independently selected from H, halogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. In an embodiment R^{17} is H. In an embodiment R^{18} is selected from H; halogen, such as Cl, or F; halo-C_{1-6}-alkyl, such as CF_3; or C_{1-6}-alkyl, such as methyl. In an embodiment R^{19} is selected from H; halogen, such as Cl, or F; halo-C_{1-6}-alkyl, such as CF_3; C_{1-6}-alkyl, such as methyl, or t-butyl; C_{1-6}-alkylsulfanyl, such as $-SCH_3$; or C_{1-6}-alkyloxy, such as methoxy. In an embodiment R^{20} is selected from H; halogen, such as Cl or F; halo-C_{1-6}-alkyl, such as CF_3; or C_{1-6}-alkyl, such as methyl. In an embodiment R^{21} is H. Typically, R^{17} and R^{21} are both H, and one or two of R^{18}, R^{19} and R^{20} is H, and the remaining substituent(s) is as defined above.

In a further embodiment of formula I R^5 is naphthyl, such as 1-naphthyl, or 2-naphthyl. In a further embodiment R^5 is naphthyl substituted with a halogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. The naphthyl may contain 1, 2, 3, 4 or 5 substituents, typically 1 or 2 substituents independently selected from the above, such as Cl, F, methyl, t-butyl, methoxy, methylsulfanyl or CF_3.

In a further embodiment of formula I R^5 is monocyclic heteroaryl, optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-

alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl, C_{1-6}-alk(en/yn)ylsulfonyl or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^{15} and R^{16} together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S or N. Typically such monocyclic heteroaryl is selected from oxathiazoles, dioxazoles, dithiazoles, oxadiazoles, thiadiazoles, triazoles, isoxazoles, oxazoles, isothiazoles, thiazoles, imidazoles, pyrazoles, pyrroles, furan(s), thiophene(s), oxathiazines, dioxazines, dithiazines, oxadiazines, thiadiazines, triazines, oxazines, thiazines, pyrazines, pyridazines, pyrimidines, oxathiins, dioxins, dithiins, pyridines, pyrans or thins.

In a further embodiment of formula I R^6 is H. In a further embodiment R^6 is C_{1-6}-alkyl, such as methyl. In a further embodiment of formula I R^6 is C_{1-6}-alk(en/yn)yloxy, such as C_{1-6}-alkyloxy, e.g. methoxy, provided that X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H, or C_{1-6} alkyl. In a further embodiment of formula I R^6 is C_{1-6}-alk(en/yn)ylsulfanyl, such as C_{1-6}-alkylsulfanyl, e.g. methylsulfanyl, provided that X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl.

In a further embodiment of formula I R^7 is H. In a further embodiment R^7 is C_{1-6}-alkyl, such as methyl, ethyl or isopropyl. In a further embodiment R^7 is C_{3-8}-cycloalk(en)yl, such as C_{3-8}-cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl.

In a further embodiment of formula I R^8 is H. In a further embodiment R^8 is C_{1-6}-alkyl, such as methyl, ethyl or isopropyl. In a further embodiment R^8 is C_{3-8}-cycloalk(en)yl, such as C_{3-8}-cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl.

In a further embodiment of formula I R^9 is H. In a further embodiment R^9 is C_{1-6}-alkyl, such as methyl, ethyl or isopropyl. In a further embodiment R^9 is hydroxy-C_{1-6}-alk(en/yn)yl, such as hydroxy-C_{1-6}-alkyl, e.g. hydroxymethyl. In a further

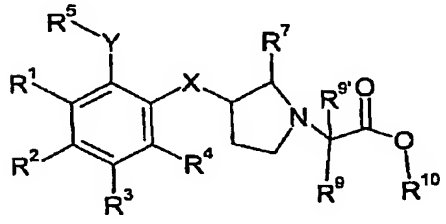
embodiment R^9 is C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl, such as C_{1-6} alkylsulfanyl-C_{1-6}-alkyl, e.g. methylsulfanylethyl.

In a further embodiment of formula I $R^{9'}$ is H. In a further embodiment $R^{9'}$ is C_{1-6}-alkyl, such as methyl, ethyl or isopropyl. In a further embodiment $R^{9'}$ is hydroxy-C_{1-6}-alk(en/yn)yl, such as hydroxy-C_{1-6}-alkyl, e.g. hydroxymethyl. In a further embodiment $R^{9'}$ is C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl, such as C_{1-6} alkylsulfanyl-C_{1-6}-alkyl, e.g. methylsulfanylethyl.

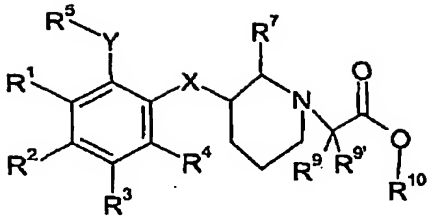
Typically, one of R^9 and $R^{9'}$ is a hydrogen, however, they may both be independently selected from C_{1-6}-alkyl, such as methyl, ethyl or isopropyl; hydroxy-C_{1-6}-alk(en/yn)yl, such as hydroxy-C_{1-6}-alkyl; or C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl, such as C_{1-6} alkylsulfanyl-C_{1-6}-alkyl.

In a further embodiment of formula I R^{10} is H.

In a further embodiment of formula I R^6 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl. To illustrate this, without limiting the invention in any way, the following sub-structures of formula I are independent embodiments of the invention:



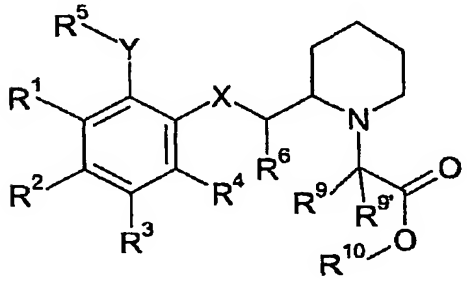
(Ib)



(Ic)

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^9, $R^{9'}$, R^{10}, X and Y are as defined in formula I above, including the described embodiments.

In a further embodiment of formula I R^7 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl. To illustrate this, without limiting the invention in any way, the following sub-structure of formula I is an embodiment of the invention:

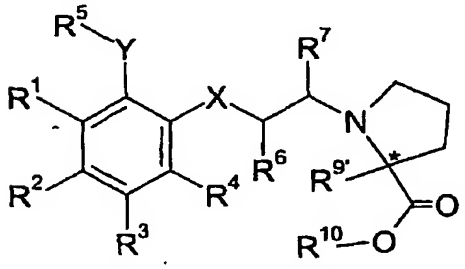


(Id)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, $R^{9'}$, R^{10}, X and Y are as defined in formula I above, including the described embodiments.

In a further embodiment of formula I R^8 and R^9 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and $R^{9'}$ is selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-

alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl. To illustrate this, without limiting the invention in any way, the following sub-structure of formula I is an embodiment of the invention:



(Ie)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, $R^{9'}$, R^{10}, X and Y are as defined in formula I above, including the described embodiments, and the asterix means that the carbon atom whereto $R^{9'}$ is attached is a chiral center. In one embodiment of formula Ie the * designates a racemic mixture of the R- and S-isomer. In a further embodiment of formula Ie the * designates the R-isomer. In a further embodiment of formula Ie the * designates the S-isomer.

In further embodiments of formula I the compound is any one of
(S)-1-{2-[2-(4-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
(S)- 1-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-{2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
(S)-1-{2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(3-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(4-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(4-Methoxy-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(3,4-Difluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
1-{2(R/S)-[2-(4-Chloro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,
1-{2(R/S)-[2-(3,4-Difluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,
(S)-1-{2-[2-(3-Fluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
1-{2(R/S)-[2-(3-Fluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,
1-{2(R/S)-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,
1-{2(R/S)-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,
({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,
2-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N--methyl-amino)-acetic acid,
({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
{2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,
({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,
(N-2-propyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,
(N-Ethyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
2-{3-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
(S)-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,
({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,
(N-2-propyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,
({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

({2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl-}N-methyl-amino)-acetic acid,
{4-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,
2-{3-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-2-propyl-amino)-acetic acid
({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
{2-[2-(4-Methylsulfanyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,
({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
(N-Methyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
2-{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
2-{3(R)-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
2-[3(R)-(2-(4-methylphenyl)-sulfanyl-phenoxy)-pyrrolidin-1-yl]-propionic acid,
{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,
2-{3(R)-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
2-{3(R)-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,
({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy)-butan-2-yl}-N-ethyl-amino)-acetic acid,
({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-butan-3-methyl-2-yl}-N-ethyl-amino)-acetic acid,
({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,
({1-[1-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,
({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-4-methyl-2-yl)}-N-ethyl-amino)-acetic acid,
({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]propan-2-yl}-N-ethyl-amino)-acetic acid,
(S)-{1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl }-N-methyl-amino)-acetic acid,

(S)-({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl)-N-ethyl-amino)-acetic acid,

({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-methyl-amino)-acetic acid,

({1-[2-(4-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,

(N-Ethyl-{1-[2-(3-fluoro-phenylsulfanyl)-phenoxymethyl]-propyl}-amino)-acetic acid,

(R)-({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-1-methyl-ethyl}-N-ethyl-amino)-acetic acid,

(S)-(2{2-[2-(4-Chloro-phenoxy)-phenoxy]-propyl-N-methyl-amino)-acetic acid,

(R)-(2{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-}-propyl-N-methyl-amino)-acetic acid,

({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-methyl-amino)-acetic acid,

({3-methyl-1-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-methyl-amino)-acetic acid,

(S)-(1{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-2-yl}N-methyl-amino)-acetic acid,

(S)-(2-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,

({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-ethyl-amino)-acetic acid,

(S)-({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-methyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl)-N-methyl-amino)-acetic acid,

({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-propan-2-yl}-N-ethyl-amino)-acetic acid,

({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-ethyl-amino)-acetic acid,

({2-[2-(4-methoxy-phenylsulfanyl)-phenoxy]-propan-1-yl}- N-Cyclohexyl -amino)-acetic acid,

{ [2-(2-(4-methylsulfanyl-phenoxy)-propan-1-yl-]-N-cyclohexyl-amino}-acetic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-cyclohexyl-amino)-acetic acid,

(S)-1-{3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propyl}-pyrrolidine-2-carboxylic acid

(S)-1-{2-[4-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[3-Chloro-2-(3-fluoro-phenylsulfunyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid,

(S)-1-{2-[5-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid,

(S)-1-[2-(5-Chloro-2-phenylsulfanyl-phenoxy)-ethyl]pyrrolidine-2-carboxylic acid,

or a pharmaceutically acceptable salt thereof. Each of these compounds is considered a specific embodiment and may be subject to individual claims.

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric,

pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures are included within the scope of the invention.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon

chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in"Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

As mentioned above, the compounds of formula I are potent inhibiters of the glycine transporter, and accordingly may be applicable for the treatment, including prevention, of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus.

Accordingly, in a further aspect the invention relates to a compound of formula I for use as a medicament.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The composition may comprise any one of the embodiments of formula I described above.

In an embodiment of the pharmaceutical composition, the compound of formula I is present in an amount of from about 0.001 to about 100 mg/kg body weight per day.

The present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of a disease or disorder, wherein an inhibitor of the glycine transport is beneficial. The medicament may comprise any one of the embodiments of formula I described above.

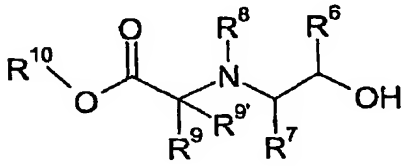
In particular the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of schizophrenia. Such schizophrenia includes both the positive and the negative symptoms of schizophrenia and other psychoses.

In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of Alzheimer's disease. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of multi-infarct dementia. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of AIDS. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of dementia. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of Huntington's disease. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of Parkinson's disease. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of amyotrophic lateral sclerosis. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of diseases wherein the brain is damaged by inner or outer influence. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of trauma to the head. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of stroke. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of convulsive disorders. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of epilepsy. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of spasticity. In a further embodiment the present invention relates to use of a compound of formula I for the preparation of a medicament for the treatment of myoclonus. In a further embodiment the present invention relates to the use of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of post-traumatic stress disorder. The medicament may comprise any one of the embodiments of formula I described above.

A further aspect of the invention relates to a method for the treatment of a disease or disorder selected from the group consisting of the positive and the negative symptoms of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus, in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

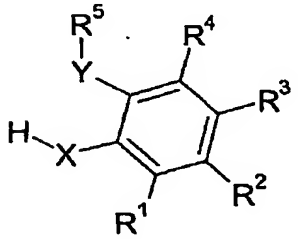
A further aspect of the invention relates to a method for the treatment of post-traumatic stress disorder in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof.

In a further aspect the present invention relates to a method of preparing a compound of formula I, comprising coupling an alcohol of formula II



(II)

with a phenol of formula III

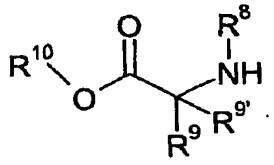


(III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, X and Y are as defined in formula I above.

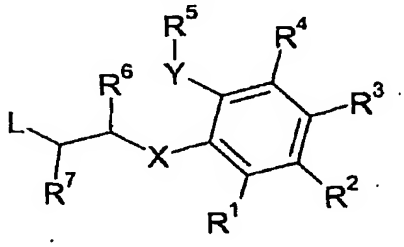
The reaction is typically performed in a suitable solvent such as tetrahydrofuran or diethyl ether containing a coupling agent such as triphenylphosphine and diethylazodicarboxylate or 1,1'-(Azodicarbonyl)dipiperidine at room temperature.

Alternatively, the present invention relates to a method of preparing a compound of formula I, comprising alkylation of an amine of formula IV



(IV)

with an alkylating agent of formula V

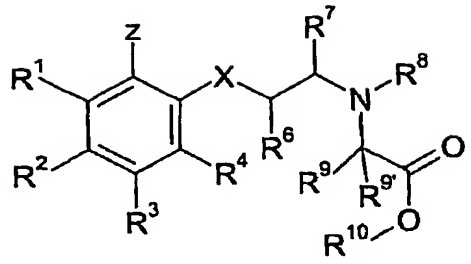


(V)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, X and Y are as defined in formula I above, and L is a suitable leaving group such as halogen, mesylate or tosylate.

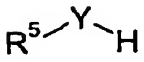
The reaction is typically performed in a suitable solvent such as ethanol, N,N-dimethylformamide or acetonitrile containing an inorganic base such as potassium or cesium carbonate or an organic base such N-ethyl diisopropylamine at an elevated temperature of 40-80 °C.

Alternatively compounds of formula I may be prepared by coupling intermediates of of formula VI where Z is an iodide, R^1-R^{10} are as described above and Y is sulfur.



(VI)

with intermediates of formula VII



(VII)

The cross coupling reaction is typically performed as described by Schopfer (Tetrahedron, **2001**, *57*, 3069-3073) where an iodide of formula IV is coupled to a thiol of formula R^5-S-H using palladium catalysis in toluene at elevated temperatures.

Compounds of formula I wherein R^{10} is hydrogen may be prepared by hydrolysis of the corresponding esters $COOR^{10}$ wherein R^{10} is an insoluble polymer or e.g: C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl. This may be performed under basic conditions, for example, using aqueous sodium hydroxide in an alcoholic solvent or under acidic conditions in the hydrolysis of a tertiary-butyl ester or cleavage from an insoluble polymer. This, method is also an aspect of the present invention.

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injetable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants, etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those

skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is a base addition salt of a compound having the utility of a free acid. When a compound of the formula (I) contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of a free acid of the formula (I) with a chemical equivalent of a pharmaceutically acceptable base. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene

and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined. amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tablette, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

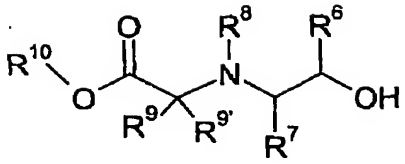
The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

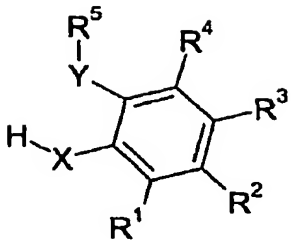
Method of preparing the compounds of formula I

The compounds of the invention are prepared by the following general methods.

Coupling of alcohol of formula II with a phenol of formula III



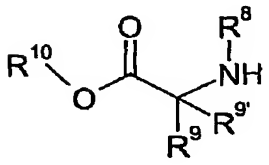
(II)



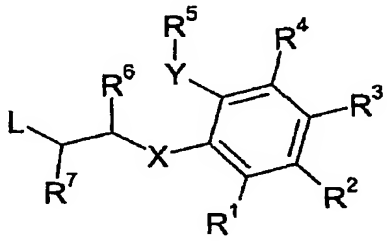
(III)

The substituents R^1-R^{10} are as defined above, X is oxygen and Y is oxygen or sulfur. The reaction is typically performed in a suitable solvent such as tetrahydrofuran or diethyl ether containing a coupling agent such as a combination of a triaryl phosphine and diethylazodicarboxylate or 1,1'-(Azodicarbonyl)dipiperidine at room temperature as described by Mitsunobu (Synthesis, 1981,1)

Alternatively compounds of the invention may be prepared by alkylation of amines of formula IV with alkylating agents of formula V.



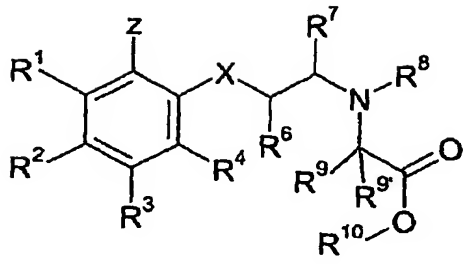
(IV)



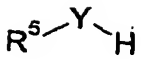
(V)

The substituents R^1-R^{10},X and Y are as defined above. L is a suitable leaving group such as halogen, mesylate or tosylate. The reaction is typically performed in a suitable solvent such as ethanol, N,N- dimethylformamide or acetonitrile containing an inorganic base such as potassium or cesium carbonate or an organic base such N-ethyl diisopropylamine at an elevated temperature of 40-80 °C.

Alternatively, compounds of the invention may be prepared by coupling intermediates of formula VI where Z is an iodide, R^1-R^{10} are as described above and Y is sulfur.



(VI)

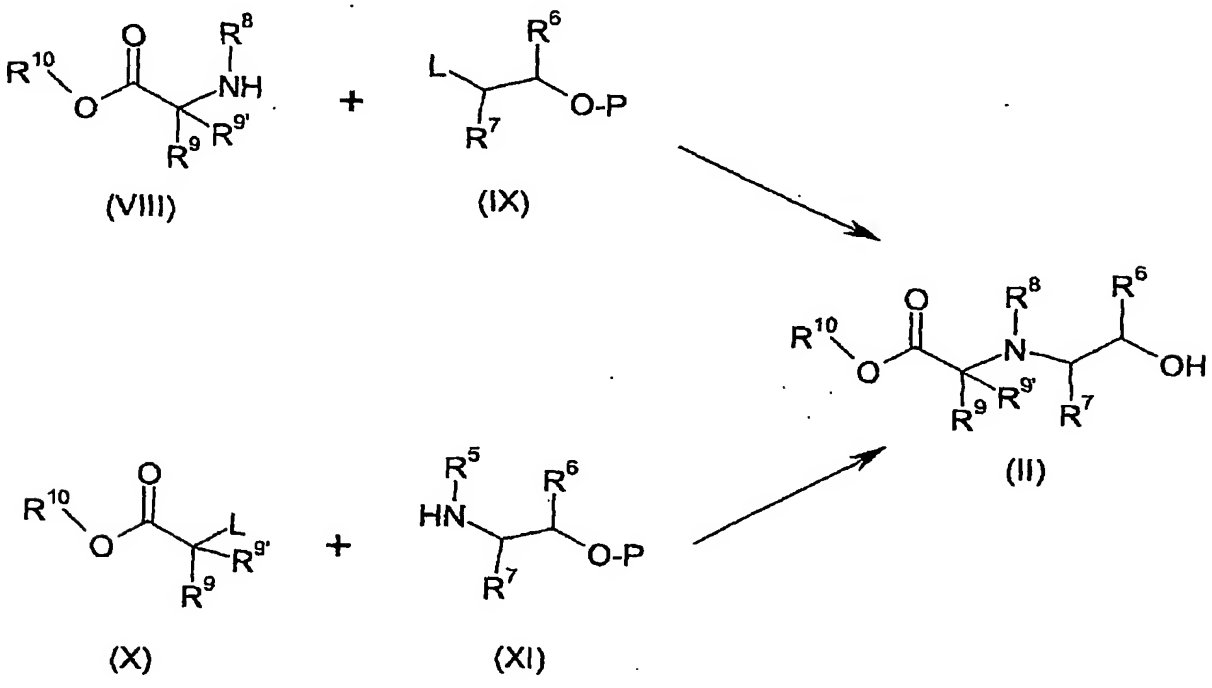


(VII)

The cross coupling reaction is typically performed as described by Schopfer (Tetrahedron, **2001**, *57*, 3069-3073) where an iodide of formula IV is coupled to a thiol of formula R^5-S-H using palladium catalysis in toluene at elevated temperatures.

Compounds of formula I wherein R^{10} is hydrogen may be prepared by hydrolysis of the corresponding esters $COOR^{10}$ wherein R^{10} is an insoluble polymer or C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl. This may be performed under basic conditions, for example, using aqueous sodium hydroxide in an alcoholic solvent or under acidic conditions in the hydrolysis of a tertiary-butyl ester or cleavage from an insoluble polymer.

Compounds of formula II may be prepared as depicted in scheme 1.



(VIII) (IX) (II)

(X) (XI)

Scheme 1

An amino acid derivative of formula VIII where R^{10}, $R^{9'}$, R^9 and R^8 are as defined above may be alkylated with an alkylating reagent of formula IX. Alternatively an acetic acid derivative of formula X where R^{10}, $R^{9'}$, R^9 are as defined above and L is a halogen, mesylate or tosylate may be reacted with an amine of formula XI where R^5, R^6 and R^7 are defined as above. The reaction is typically performed in a suitable solvent such as ethanol, N,N- dimethylformamide,DMSO or acetonitrile containing an inorganic base such as potassium or cesium carbonate or an organic base such N-ethyl diisopropylamine at an elevated temperature of 40-150 °C. P may be hydrogen or a suitable protecting group for an alcohol known to those skilled in the art. This could for example be tert-butyl dimethyl silyl or tetrahydropyranyl. The methods for the protection and deprotection of alcohols are described in the textbook *Protective Groups in Organic Synthesis*, T.W.Greene and p.G.M. Wuts, Wiley Interscience, (1991) ISBN 0571623016

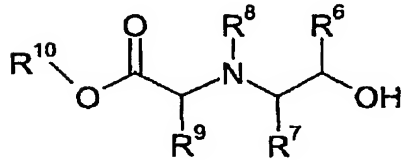
Intermediates of formula III were prepared from 2-cyclohexanone as described by Samoshin et al. (*Tet. Lett.* **1994** , *35*, 7413-7414). Alternatively an appropiately substituted 2-halo-anisole may be metallated with an alkaline metal such as magnesium (Gilman, *Recl. Trav. Chim. Pays-Bas* **1935**, 588) or lithium (Hader et al, *J.Organomet.Chem.* **1989**, *364*, 1-16) and reacted with bis aryl bissulfides. Alternatively 2-halo-anisoles in the case of the halogen being iodide may be coupled using palladium/phosphine catalysis with a thiophenol as described in the general method of Schopfer (*Tetrahdron* **2001**, *57* , 3069-3073 to give intermediates, after demethylation of the anisole, of formula III.

Intermediates of formula IV are typically commercially available or their syntheses are well described in the literature.

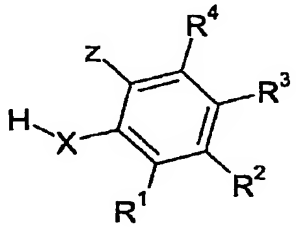
Compounds of formula V where X is O may be prepared by reacting intermediates of formula III with trimethylene carbonate to give the O-hydroxyethyl derivative which can then be converted to compounds of formula V. Where L is Cl this could be using carbon tetrachloride and triphenylphosphine in dichloromethane. In the case of tosylate and mesylate this could by the use of tosyl chloride or methane sulfonyl

chloride respectively in a solvent such as dichloromethane or tetrahydrofuran. These methods are standard to those skilled in the art. Compounds of formula V where X is carbon may be prepared by the alkylation of suitably substituted 2-iodo-benzylhalides with diethyl malonate in the general procedure described by L.F. Fieser, E. Berliner, *J. Am. Chem. Soc.* **1952**, *74*, 536 to give 2-iodo-phenylpropionic acids. In the case of X is sulfur, coupling with an appropiate thiophenol using copper catalysis according to the method of Bartl et al , *Collection Czechoslovak Chem. Commun.* **1981**, *46*, 141 affords the 2-(arylsulfanyl)phenyl propionic acid which can be reduced using standard methods such as borane-tetrahydrofuran complex or lithium aluminium hydride to 2-(arylsulfanyl)phenyl propanol. Activation of the alcohol to nucleophilic displacement can be performed as described above.

Compounds of formula VI may be prepared by the reaction of intermediates of formula II with intermediates of formula XII. The substituents R^1-R^{10} are as defined above, X is oxygen, sulphur or $CR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined above, and Z is an iodide. The reaction is typically performed in a suitable solvent such as tetrahydrofuran or diethyl ether containing a coupling agent such as triphenyl phosphine and diethylazodicarboxylate or 1,1'-(Azodicarbonyl)dipiperidine at room temperature.



(II)



(XII)

Intermediates of formula XII where Z is an iodide are commercially available or can be easily obtained by demethylation of the corresponding 2-iodo-anisole using for example boron tribromide in toluene or similar methods well known to those skilled in the art. Alternatively treatment of the corresponding anisole with tert-butyl lithium and quenching with iodine as descrived by Iwao (*J. Org. Chem.* **1990**, *55*, 3622-3627)

and subsequent demethylation will also provide intermediates of formula XII. A third approach is the conversion of the appropiate 2-methoxy aniline derivative to the iodide in a Sandmeyer reaction as described by Still (*J. Org. Chem.* **1987**, *52*, 748-753), followed by demethylation to give intermediates of formula XII. These methods are all well described in the literature.

Examples

General Methods

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.
Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated methylenchloride (99.8%D), chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

For ion-exchange chromatography, the following material was used: SCX-columns (1 g) from Varian Mega Bond Elut®, Chrompack cat. No. 220776. Prior to use, the

SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL). For de-complexation by irradiation, a ultaviolet light source (300 W) from Philipps was used.

Polymerbound PPh_3 (0.93 mmol/g, 100-200 mesh) was purchased from Senn Chemicals.

Preparation of Intermediates of Formula XI

1-Cyclohexylamino-propan-2-ol

Cyclohexanone (0.98 g, 10mmol) and 1-amino-propan-2-ol (0.75g, 10 mmol) were mixed and MeOH (20 mL), acetic acid (12 mg, 0.5 mmol), cyanoborohydride resin (7 g, 14 mmol, 2 mmol/g, prepared as described by A.R. Sande et al, *Tetrahedron Letters* **1984**, 3501) were added. The reaction mixture was heated under reflux for 16 h. The resin was filtered off and the filtrate was evaporated *in vacuo*. The crude product was used without further purification.

2-(tert-Butyl-dimethyl-silanyloxy)-propylamine

tert-Butyl-chloro-dimethyl-silane (2.6 g 17 mmol) was dissolved in DCM (20 mL). 1-Amino-propan-2-ol (1.2 g, 16 mmol), triethylamine (2.2 mL, 16 mmol) and a catalytic amount of DMAP were added. The reaction mixture was stirred for 16 h. Water (10 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The product was isolated as an oil. Yield: 2.4 g, 80%.

The following intermediates were prepared in an analogous fashion:

2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethylamine

1-(tert-Butyl-dimethyl-silanyloxymethyl)-propylamine

1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-methyl-propylamine

1-(S)-2-(tert-Butyl-dimethyl-silanyloxy)-)-methyl-ethylamine

1-(R)-2-(tert-Butyl-dimethyl-silanyloxy)- methyl-ethylamine

Preparation of Intermediates of Formula II

(2-Hydroxymethyl-piperidin-1-yl)-acetic acid tert-butyl ester

Bromo-acetic acid *tert*-butyl ester (0.39 g, 2 mmol) was dissolved in DMF (1 mL). A solution of piperidin-2-yl-methanol (0.25 g, 2.2 mmol) in DMF (1 mL) and diisopropylethylamine (0.38 mL, 2.2 mmol) was added. The reaction mixture was stirred at 50°C for 16 h. The solvent was removed *in vacuo*. EtOAc (20 mL) and water (7 mL) was added. The two phases were separated. The aqueous phase was extracted twice with EtOAc (20 mL). The combined EtOAc phases were dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The product was isolated as an oil. Yield: 0.37 g, 80%.

The following intermediates were prepared in an analogous fashion:

[(2-Hydroxy-ethyl)-methyl-amino]-acetic acid tert-butyl ester

[Ethyl-(2-hydroxy-ethyl)-amino]-acetic acid tert-butyl ester

[(2-Hydroxy-ethyl)-isopropyl-amino]-acetic acid tert-butyl ester

(4-Hydroxy-piperidin-1-yl)-acetic acid tert-butyl ester

(3-Hydroxy-pyrrolidin-1-yl)-acetic acid tert-butyl ester

(R)-(3-Hydroxy-pyrrolidin-1-yl)-acetic acid tert-butyl ester

2-(3-Hydroxy-pyrrolidin-1-yl)-propionic acid tert-butyl ester

(S)-(3-Hydroxy-pyrrolidin-1-yl)-acetic acid tert-butyl ester

(S)-2-(3-Hydroxy-pyrrolidin-1-yl)-propionic acid tert-butyl ester

[Cyclohexyl-(2-hydroxy-propyl)-amino]-acetic acid tert-butyl ester

[2-(tert-Butyl-dimethyl-silanyloxy)-propylamino]-acetic acid tert-butyl ester

2-(tert-Butyl-dimethyl-silanyloxy)-propylamine (6.0 g, 31.6 mmol) was dissolved in DMF (60 mL). Diisopropylethylamine (5.5 mL, 31.6 mmol) and bromo-acetic acid *tert*-butyl ester (3.6 g, 18.6 mmol) was added. The reaction mixture was stirred at 50 °C for 16 h. The mixture was evaporated onto silica gel and and purified by column chromatography using a gradient, starting eluting with ethyl acetate/heptane 20:80 up to ethyl acetate/heptane 80:20. The product was isolated as an oil. Yield: 4.0 g, 71%.

The following intermediates were prepared in an analogous fashion:

[2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethylamino]-acetic acid tert-butyl ester
[1-(tert-Butyl-dimethyl-silanyloxymethyl)-propylamino]-acetic acid tert-butyl ester
[1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-methyl-propylamino]-acetic acid tert-butyl ester
(S)-[2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethylamino]-acetic acid
(R)-[2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethylamino]-acetic acid tert-butyl ester

[Ethyl-(2-hydroxy-propyl)-amino]-acetic acid tert-butyl ester

[2-(tert-Butyl-dimethyl-silanyloxy)-propylamino]-acetic acid tert-butyl ester (1.2 g, 4 mmol) and diisopropylethylamine (9.7 mL, 56 mmol) was dissolved in DMF (20 mL). Iodo-ethane (2.6 mL, 32 mmol) was added. The reaction was stirred at 50 °C for 16 h. The solvent was removed *in vacuo*. The crude product was dissolved in EtOAc (100 mL) and the solution was washed with water (20 mL). The organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*.
The residue was dissolved in acetonitrile (30 mL) and Et_3N 3HF (1.3 mL, 8 mmol) was added. The reaction was stirred for 16 h. The solvent was removed *in vacuo*. The crude product was dissolved in EtOAc (100 mL) and washed with saturated sodium bicarbonate solution (25 mL) and saturated sodium chloride solution (25 mL). The organic phase was dried over magnesium sulfate and the solution was slowly filtered through 5 g of silica gel. The filtrate was evaporated *in vacuo*. Yield: 0.17 g, 20%.

The following intermediates were prepared in an analogous fashion:
[Ethyl-(2-hydroxy-1-methyl-ethyl)-amino]-acetic acid tert-butyl ester
[Ethyl-(1-hydroxymethyl-propyl)-amino]-acetic acidtert-butyl ester
[Ethyl-(1-hydroxymethyl-2-methyl-propyl)-amino]-acetic acid tert-butyl ester
(S)-[Ethyl-(2-hydroxy-1-methyl-ethyl)-amino]-acetic acid tert-butyl ester
(R)-[Ethyl-(2-hydroxy-1-methyl-ethyl)-amino]-acetic acid tert-butyl ester

Preparation of Intermediates of Formula II

[(1-Hydroxymethyl-2-methyl-propyl)-methyl-amino]-acetic acid tert-butyl ester
{[1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-methyl-propyl]-amino}-acetic acid tert-butyl ester (1.9 g, 6.1 mmol) and diisopropylethylamine (4.2 mL, 24 mmol) were

dissolved in DMF (15 mL). A solution of MeI (0.45 mL, 7.3 mmol) in DMF (100 mL) was slowly added over 15 min. The reaction was stirred for 2½ h. The solvent was removed *in vacuo*. The residue product was dissolved in EtOAc (100 mL) and the solution was washed with water (20 mL). The organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in acetonitrile (45 mL) and Et_3N 3HF (2 mL, 12.3 mmol) was added. The reaction was stirred for 16 h. The solvent was removed *in vacuo*. The crude product was dissolved in EtOAc (100 mL) and washed with saturated sodium bicarbonate solution (25 mL) and saturated sodium chloride solution (25 mL). The organic phase was dried over magnesium sulfate and the solution was slowly filtered through 5 g of silica gel. The filtrate was evaporated *in vacuo*. Yield: 1.1 g, 78%.

The following intermediates were prepared in an analogous fashion:

[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-acetic acid tert-butyl ester
[(1-Hydroxymethyl-propyl)-methyl-amino]-acetic acid tert-butyl ester
(S)-[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-acetic acid tert-butyl ester
(R)-[(2-Hydroxy-1-methyl-ethyl)-methyl-amino]-acetic acid tert-butyl ester
[(2-Hydroxy-propyl)-methyl-amino]-acetic acid tert-butyl ester

Preparation of Intermediates of Formula II using Intermediates of Formula VIII and Intermediates of Formula IX

(2-Hydroxy-ethyl)-pyrrolidine-2(S)-carboxylic acid tert-butyl ester

L-Pyrrolidine-2-carboxylic acid *tert*-butyl ester (0.41 g, 2.4 mmol) was dissolved in DMF (2 mL) containing diisopropylethylamine (1.25 mL, 7.2 mmol). A solution of 2-bromo-ethanol (0.34 mL, 4.8 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 70°C for 16 h. The solvent was removed *in vacuo*. EtOAc (20 mL) and saturated sodium bicarbonate solution (10 mL) was added. The aqueous phase was extracted twice with EtOAc (20 mL). The combined EtOAc phases were dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The product was isolated as an oil. Yield: 0.37 g, 72%.

The following intermediate was prepared in an analogous fashion:

1-(2-Hydroxy-propyl)-pyrrolidine-2(S) -carboxylic acid tert-butyl ester

Preparation of Intermediates of Formula III

2-(4-Chloro-phenoxy)-phenol

The compound was synthesised as described by G.W. Yeager, D.N. Schissel, *Synthesis* **1995**, 28-30.

The following intermediates were prepared in an analogous fashion:

2-(3,4-Difluoro-phenoxy)-phenol

2-(3-Fluoro-phenoxy)-phenol

2-(3-Chloro-phenoxy)-phenol

2-(4-Methoxy-phenoxy)-phenol

3-Chloro-2-iodoanisole

A solution of 3-chloroanisole (1.753 g, 12.3 mmol) in THF (60 mL) was cooled to –95 °C. A solution of *sec*-BuLi in cyclohexane (1.3M, 9.5 mL, 12.4 mmol) was added dropwise keeping the internal temperature below –90 °C. After 1h a solution of I_2 (3.15 g, 12.4 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to reach room temperature overnight. Diethylether (100 mL) was added. The organic layer was washed with 1M aqueous Na_2SO_3, H_2O, brine and dried over Na_2SO_4. The crude product was adsorbed onto silica gel. After purification by flash chromatography using silica gel, eluting with heptanes/EtOAc, 98:2, the product was obtained as colorless crystals Yield : 2.19g, 66%.

3-Chloro-2-(3-fluoro-phenylsulfanyl)-phenol

A dry round bottomed flask was charged with NaO^tBu (398 mg, 4.14 mmol), CuI (62 mg, 0.33 mmol), neocuproin (66 mg, 0.30 mmol), 3-fluoro-thiophenol (394 mg, 3.07 mmol) and 3-chloro-2-iodoanisole (698 mg, 2.60 mmol). The flask was evacuated and backfilled with Ar three times. Dry toluene (10 mL) was added and the mixture stirred at 105 °C overnight. The mixture was diluted with toluene (40 mL) and filtered

through a pad of silica gel and evaporated to dryness to give a quantitative yield of crude *1-Chloro-2-(3-fluoro-phenylsulfanyl)-3-methoxy-benzene.* The material was dissolved in toluene (20 mL) and cooled to 0 °C. Neat BBr_3 (0.38 mL, 4.02 mmol) was added dropwise and the mixture was allowed to reach room temperature overnight. The mixture was quenched by the addition of H_2O / ice (80 mL) and diethyl ether (100 mL). The organic layer was washed with brine. After drying over Na_2SO_4 the crude product was adsorbed onto silica gel. After flash chromatography using silica gel, eluting with heptanes/EtOAc, 96:4 the title compound was obtained as a yellow oil Yield: 642 mg, 97% over two steps.

4-Chloro-1-(3-fluoro-phenylsulfanyl)-2-methoxybenzene

A dry round bottomed flask was charged with KO^{t}Bu (1.903 g, 17.0 mmol), 5-chloro-2-iodoanisole (4.054 g, 15.1 mmol), Pd_2dba_3 (144 mg, 0.16 mmol), DPEPhos (176 mg, 0.33 mmol) and 3-fluoro-thiophenol (1.903 g, 17.0 mmol). The flask was evacuated and backfilled with Ar three times. Dry toluene (80 mL) was added and the mixture stirred at 95 °C for 2 h. The mixture was filtered through a pad of silica gel followed by adsorption onto silica gel. After purification by flash chromatography using silica gel, eluting with heptanes/EtOAc, 97:3, the title compound was obtained as a yellow oil (3.41 g, 85%).

5-Chloro-2-(3-fluoro-phenylsulfanyl)-phenol

A solution of 4-chloro-1-(3-fluoro-phenylsylfanyl)2-methoxybenzene (3.12 g, 11.6 mmol) in dry toluene (60 mL) was cooled to 0 °C. Neat BBr_3 (1.50 mL, 15.9 mmol) was added dropwise and the mixture was allowed to reach room temperature overnight. The mixture was quenched by the addition of H_2O / ice (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethylether (2x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and adsorbed onto silica gel. After flash chromatography using silica gel, eluting with heptanes/EtOAc, 95:5, the title compound was obtained as a light yellow oil (2.26 g, 77%).

The following phenols were prepared in an analogous fashion:

2-Chloro-6-(3-fluoro-phenylsulfanyl)-phenol

4-Chloro-2-(3-fluoro-phenylsulfanyl)-phenol

Preparation of Intermediates V for Example 2

2-(2-Iodo-benzyl)-malonic acid diethyl ester

Sodium (0.19 g, 8.2 mmol) was dissolved in absolute ethanol (12 mL). The solution was cooled on an ice bath. Malonic acid diethyl ester (1.3 g, 8.1 mmol) was added. A solution of 1-chloromethyl-2-iodo-benzene (2.0 g, 7.9 mmol) in absolute ethanol (6 mL) cooled on an ice bath was added to the malonic acid diethyl ester solution. The solution, which deposited sodium chloride, was let stand at 0 °C for 4 h and at room temperature overnight. The solution was neutralised with HCl (4N). The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (25 mL). Water (15 mL) was added and the phases were separated. The aqueous phase was reextracted with dichloromethane (10 mL). The combined organic fractions were dried (Na_2SO_4), filtered and evaporated. Yield: 2.86 g, 92%.

3-(2-Iodo-phenyl)-propionic acid

Concentrated HCl (2.3 mL) and water (0.3 mL) was added to 2-(2-iodo-benzyl)-malonic acid diethyl ester (1.4 g, 3.6 mmol) and the mixture was refluxed overnight. Starting material could still be seen on TLC. More concentrated HCl (2 mL) was added and the mixture was refluxed overnight. Water (20 mL) and ether (50 mL) was added to the mixture. The two phases was separated. The organic phase was extracted with an ammonium hydroxide solution (5N, 30 mL). The basic water phase was added slowly to ice-cold conc. HCl. The white precipitate was filtered and washed with ice-cold water and the solvent was removed *in vacuo*. Yield: 0.32 g, 32%.

3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propionic acid

3-(2-Iodo-phenyl)-propionic acid (0.3 g, 1.1 mmol) was dissolved in water (2.8 mL). 3-Fluoro-benzenethiol (0.13 g, 0.99 mmol), KOH (0.15 g, 2.6 mmol) and Cu (13 mg, 0.2 mmol) was added. The mixture was refluxed overnight. The hot solution was filtered and the filtrate was made acidic with concentrated HCl. The mixture was extracted with dichloromethane (2 x 25 mL). The combined organic phases were

washed with water (15 mL), dried ($MgSO_4$), filtered and evaporated. Yield: 0.26 g, 96 %.

3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propan-1-ol

$LiAlH_4$ (46 mg, 1.22 mmol) was suspended in ether (1.7 mL). A solution of 3-[2-(3-fluoro-phenylsulfanyl)-phenyl]-propionic acid (2.6 g, 0.94 mmol) in ether (1.7 mL) was added slowly. The reaction was stirred for 4 h at room temperature. Excess $LiAlH_4$ was hydrolysed with water. The mixture was made acidic using HCl (4N). Ether (20 mL) was added. The two phases were separated and the organic phase was washed with NaOH (2N) and then with water. The organic phase was dried ($MgSO_4$), filtered and evaporated. Yield: 0.14 g, 55%.

1-(3-Iodo-propyl)-2-(3-fluro-phenylsulfanyl)-benzene

Polymerbound PPh_3 (0.49 g, 0.46 mmol) was suspended in dichloromethane (4.5 mL). Imidazole (0.03 g, 0.46 mmol) and I_2 (0.12 g, 0.46 mmol) was added and the mixture was stirred for 5 minutes. A solution of 3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propan-1-ol (0.096 g, 0.37 mmol) in dichloromethane (0.5 mL) was added and the mixture was stirred for 4 h at room temperature. The resin was filtered off and washed with dichloromethane (2 mL). The filtrate was washed with $Na_2S_2O_3$ (2X 2 mL) and water (2 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated. Yield: 0.096 g, 71%.

Preparation of Intermediate of Formula VI for Example 4

(S)-1-[2-(5-Chloro-2-iodo-phenoxy)-ethyl]-pyrrolidine-2-carboxylic acid tert-butyl ester

5-Chloro-2-iodophenol (801 mg, 3.15 mmol) and PPh_3 (1.15 g, 4.41 mmol) were dissolved in THF (25 mL). DIAD (0.91 mL, 4.62 mmol). was added dropwise and the solution was stirred for 20 min. A solution of 1-(2-hydroxy-ethyl)-pyrrolidine-2-(*S*)-carboxylic acid *tert* butyl ester (816 mg, 3.79 mmol) in THF (4 mL) was added via canulation. The mixture was stirred for 40 min at 0 °C then for 1.5 h at room temperature and finally for 3 h at 50 °C. The mixture was diluted with heptanes (100 mL), washed with water (4x 25 mL), dried over Na_2SO_4 and evaporated onto silica

gel. After flash chromatography using silica gel, eluting with heptanes/EtOAc, 9:1, the title compound was obtained as a colorless oil (1.023 g, 72%).

Preparation of compounds of the invention

Example 1

1aa (S)-1-{2-[2-(4-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid

A solution of L-1-(2-Hydroxy-ethyl)-pyrrolidine-2-carboxylic acid tert-butyl ester (0.068 mmol) in THF (0.5 mL) was added to polymerbound PPh_3 (75 mg, 0.07mmol). A solution of 2-(3-Fluoro-phenylsulfanyl)-phenol (0.04 mmol) in THF (0.5 mL) and a solution of DEAD (0.068 mmol) in THF (0.5 mL) added. The reaction was stirred at room temperature for 16 h. The resin was filtered off and washed with methanol (2 x 1 mL) and THF (1 mL). The solvents were removed by evaporation in vacuo. HCl in acetic acid (1 M, 1.5 mL) was added and the mixture was stirred for 16 h. The solvent was removed *in vacuo*. The crude product was purified by preparative LC-MS.
LC/MS (m/z) 362.2 (MH^+); RT = 1.97; purity (UV, ELSD): 93%, 100%; yield: 7.5 mg.

The following compounds were prepared in an analogous fashion:

***1ab** (S)-1-{2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,*
LC/MS (m/z) 400.1 (MH^+); RT = 2.45; purity (UV, ELSD): 96%, 100%; yield: 6.2 mg.

1ac (S)-1-{2-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
LC/MS (m/z) 412.0 (MH^+); RT = 2.21; purity (UV, ELSD): 99%, 100%; yield: 5.5 mg.

1ad (S)- 1-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

LC/MS (m/z) 362.2 (MH^+); RT = 1.98; purity (UV, ELSD): 95%, 100%; yield: 4.8 mg.

1ae (S)-{2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
LC/MS (m/z) 378.1 (MH^+); RT = 2.12; purity (UV, ELSD): 93%, 100%; yield: 5.1mg.

1af (S)-1-{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
LC/MS (m/z) 378.1 (MH^+); RT = 2.10; purity (UV, ELSD): 98%, 100%; yield: 3.3mg.

1ag (S)-1-{2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
LC/MS (m/z) 412.0 (MH^+); RT = 2.28; purity (UV, ELSD): 99%, 100%; yield: 5.2mg.

1ah (S)-1-{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
LC/MS (m/z) 396.1 (MH^+); RT = 2.15; purity (UV, ELSD): 98%, 100%; yield: 4.5mg.

1ai (S)-1-{2-[2-(3-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
LC/MS (m/z) 362.1 (MH^+); RT = 2.02; purity (UV, ELSD): 96%, 100%; yield: 12.1mg.

1aj (S)-1-{2-[2-(4-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
LC/MS (m/z) 362.2 (MH^+); RT = 2.12; purity (UV, ELSD): 95%, 99%; yield: 12.7mg.

1ak (S)-1-{2-[2-(4-Methoxy-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

LC/MS (m/z) 358.0 (MH^+); RT = 1.83; purity (UV, ELSD): 100%, 99%; yield: 13.8mg.

1al (S)-1-{2-[2-(3,4-Difluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

LC/MS (m/z) 364.2 (MH^+); RT = 1.95; purity (UV, ELSD): 100%, 99%; yield: 13.8mg.

1am 1-{2(R/S)-[2-(4-Chloro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

LC/MS (m/z) 376.1 (MH^+); RT = 2.12; purity (UV, ELSD): 99%, 99%; yield: 4.1mg.

1an 1-{2(R/S)-[2-(3,4-Difluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

LC/MS (m/z) 378.1 (MH^+); RT = 2.07; purity (UV, ELSD): 96%, 99%; yield: 3.4mg.

1ao (S)-1-{2-[2-(3-Fluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

LC/MS (m/z) 346.2 (MH^+); RT = 1.99; purity (ELSD): 95%; yield: 3.44mg.

1ap 1-{2(R/S)-[2-(3-Fluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

LC/MS (m/z) 360.3 (MH^+); RT = 2.02; purity (UV, ELSD): 70%, 98%; yield: 7.2mg.

1aq 1-{2(R/S)-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

LC/MS (m/z) 376.1 (MH^+); RT = 2.10; purity (UV, ELSD): 99%, 98%; yield: 4.3mg.

1ar 1-{2(R/S)-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

LC/MS (m/z) 392.2 (MH^+); RT = 2.23; purity (UV, ELSD): 94%, 88.9%; yield: 2.1mg.

1as ({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 388.2 (MH^+); RT = 2.53; purity (UV, ELSD): 94%, 95%; yield: 5.6mg

1at 2-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
LC/MS (m/z) 400.0 (MH^+); RT = 2.40; purity (UV, ELSD): 94%, 100%; yield: 4.2mg

1au ({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N--methyl-amino)-acetic acid,
LC/MS (m/z) 351.9 (MH^+); RT = 2.02; purity (UV, ELSD): 98%, 100%; yield: 9.9mg

1av ({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
LC/MS (m/z) 370.0 (MH^+); RT = 2.07; purity (UV, ELSD): 93%, 100%; yield: 6.7mg

1aw {2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,
LC/MS (m/z) 414.4 (MH^+); RT 2.52= ; purity (UV, ELSD): 100%, 100%; yield: 2.6mg

1ax ({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,
LC/MS (m/z) 336.2 (MH^+); RT = 1.96; purity (UV, ELSD): 96%, 95%; yield: 1.8mg

1ay {4-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,
LC/MS (m/z) 400.0 (MH^+); RT = 2.48; purity (UV, ELSD): 89%, 100%; yield: 5.5mg

1az (N-2-propyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
LC/MS (m/z) 414.2 (MH^+); RT = 2.26; purity (UV, ELSD): 95%, 100%; yield: 2.4mg

1ba ({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 400.1 (MH^+); RT = 2.27; purity (UV, ELSD): 99%, 100%; yield: 8.3mg

1bb (N-Ethyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,
LC/MS (m/z) 378.3 (MH^+); RT = 2.13; purity (UV, ELSD): 99%, 100%; yield: 8.5mg

1bc *2-{3-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,*
LC/MS (m/z) 412.0 (MH^+); RT = 2.25; purity (UV, ELSD): 100%, 100%; yield: 7.5mg

1bd *(S)-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,*
LC/MS (m/z) 386.0 (MH^+); RT = 2.42; purity (UV, ELSD): 90%, 95%; yield: 2.2mg

1be *({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,*
LC/MS (m/z) 384.2 (MH^+); RT = 2.15; purity (UV, ELSD): 97%, 100%; yield: 8.2mg

1bf *(N-2-propyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,*
LC/MS (m/z) 392.2 (MH^+); RT = 2.17; purity (UV, ELSD): 97%, 99%; yield: 9.9mg

1bg *{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,*
LC/MS (m/z) 386.0 (MH^+); RT = 2.38; purity (UV, ELSD): 96%, 100%; yield: 3.1mg

1bh *({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,*
LC/MS (m/z) 366.2 (MH^+); RT = 2.10; purity (UV, ELSD): 100%, 100%; yield: 11.5mg

1bi *({2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl-}N-methyl-amino)-acetic acid,*
LC/MS (m/z) 352.2 (MH^+); RT = 2.12; purity (UV, ELSD): 78%, 97%; yield: 2.2mg

1bj *{4-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,*
LC/MS (m/z) 412.1 (MH^+); RT = 2.32; purity (UV, ELSD): 99%, 100%; yield: 5.9mg

1bk *2-{3-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,*
LC/MS (m/z) 412.1 (MH^+); RT = 2.17; purity (UV, ELSD): 99%, 100%; yield: 6.1mg

1bl *({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-2-propyl-amino)-acetic acid*

LC/MS (m/z) 402.2 (MH^+); RT = 2.57; purity (UV, ELSD): 90%, 98%; yield: 8.3mg

1bm *({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,*

LC/MS (m/z) 373.8 (MH^+); RT = 2.34; purity (UV, ELSD): 91%, 100%; yield: 8.9mg

1bn *{2-[2-(4-Methylsulfanyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,*

LC/MS (m/z) 404.2 (MH^+); RT = 2.21; purity (UV, ELSD): 98%, 100%; yield: 2.6mg

1bo *({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,*

LC/MS (m/z) 385.8 (MH^+); RT = 2.19; purity (UV, ELSD): 95%, 100%; yield: 8.1mg

1bp *(N-Methyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,*

LC/MS (m/z) 386.0 (MH^+); RT = 2.13; purity (UV, ELSD): 95%, 100%; yield: 5.3mg

1bq *-2-{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid*

LC/MS (m/z) 400.1 (MH^+); RT = 2.44; purity (UV, ELSD): 97%, 100%; yield: 9.2mg

1br *2-{3(R)-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,*

LC/MS (m/z) 412.1 (MH^+); RT = 2.26; purity (UV, ELSD): 100%, 98%; yield: 9.4mg

1bs *2-[3(R)-(2-(4-methylphenyl)-sulfanyl-phenoxy)-pyrrolidin-1-yl]-propionic acid,*

LC/MS (m/z) 358.2 (MH^+); RT = 2.06; purity (UV, ELSD): 98%, 98%; yield: 8.1mg

1bt *{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,*

LC/MS (m/z) 386.2 (MH^+); RT = 2.38; purity (UV, ELSD): 94%, 99%; yield: 3.0mg

1bu 2-{3(R)-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
LC/MS (m/z) 412.2 (MH^+); RT = 2.20; purity (UV, ELSD): 98%, 100%; yield: 9.5mg

1bv 2-{3(R)-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,
LC/MS (m/z) 378.1 (MH^+); RT = 2.13; purity (UV, ELSD): 91%, 100%; yield: 6.3mg

1bw ({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 394.2 (MH^+); RT = 2.29; purity (UV, ELSD): 97%, 99%; yield: 4.8mg

1bx({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy)-butan-2-yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 428.1 (MH^+); RT = 2.46; purity (UV, ELSD): 94%, 100%; yield: 4.6mg

1by ({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-butan-3-methyl-2-yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 442.2 (MH^+); RT = 2.56; purity (UV, ELSD): 96%, 100%; yield: 1.0mg

1bz ({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 412.1 (MH^+); RT = 2.32; purity (UV, ELSD): 99%, 100%; yield: 4.7mg

1ca ({1-[1-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 380.1 (MH^+); RT = 2.18; purity (UV, ELSD): 99%, 100%; yield: 4.8mg

1cb ({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-4-methyl-2-yl)}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 426.2 (MH^+); RT = 2.42; purity (UV, ELSD): 90%, 100%; yield: 0.9mg

1cc ({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]propan-2-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 398.2 (MH^+); RT = 2.12; purity (UV, ELSD): 96%, 100%; yield: 3.1mg

1cd (S)-{1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl }-N-methyl-amino)-acetic acid ,

LC/MS (m/z) 366.2 (MH^+); RT = 2.08; purity (UV, ELSD): 98%, 97%; yield: 4.4mg

1ce (S)-({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl)-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 380.2 (MH^+); RT = 2.18; purity (UV, ELSD): 72%, 100%; yield: 1.3mg

1cf ({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 416.2 (MH^+); RT = 2.34; purity (UV, ELSD): 100%, 100%; yield: 4.9mg

1cg ({1-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 380.3 (MH^+); RT = 2.19; purity (UV, ELSD): 94%, 100%; yield: 3.9mg

1ch ({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-methyl-amino)-acetic acid,

LC/MS (m/z) 380.2 (MH^+); RT = 2.21; purity (UV, ELSD): 98%, 100%; yield: 3.6mg

1ci ({1-[2-(4-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 394.3 (MH^+); RT = 2.33; purity (UV, ELSD): 96%, 100%; yield: 4.5mg

1cj (N-Ethyl-{1-[2-(3-fluoro-phenylsulfanyl)-phenoxymethyl]-propyl}-amino)-acetic acid,

LC/MS (m/z) 378.3 (MH^+); RT = 2.16; purity (UV, ELSD): 99%, 100%; yield: 5.7mg

1ck (R)-({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-1-methyl-ethyl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 416.0 (MH^+); RT = 2.35; purity (UV, ELSD): 92%, 100%; yield: 1.5mg

1cl (S)-(2{2-[2-(4-Chloro-phenoxy)-phenoxy]-propyl-N-methyl-amino)-acetic acid,
LC/MS (m/z) 350.1 (MH^+); RT = 2.00; purity (UV, ELSD): 96%, 97%; yield: 2.6mg

1cm (R)-(2{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-}-propyl-N-methyl-amino)-acetic acid,,
LC/MS (m/z) 366.1 (MH^+); RT = 2.10; purity (UV, ELSD): 98%, 98%; yield: 6.1mg

1cn ({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,
LC/MS (m/z) 350.1 (MH^+); RT = 1.97; purity (UV, ELSD): 81%, 99%; yield: 2.2mg

1co ({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 380.3 (MH^+); RT = 2.19; purity (UV, ELSD): 97%, 98%; yield: 2.9mg

1cp ({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-methyl-amino)-acetic acid,
LC/MS (m/z) 394.2 (MH^+); RT = 2.31; purity (UV, ELSD): 93%, 100%; yield: 2.3mg

1cq ({3-methyl-1-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,
LC/MS (m/z) 442.3 (MH^+); RT = 2.46; purity (UV, ELSD): 98%, 100%; yield: 1.7mg

1cr ({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-methyl-amino)-acetic acid,
LC/MS (m/z) 398.1 (MH^+); RT = 2.24; purity (UV, ELSD): 96%, 98%; yield: 8.1mg

1cs (S)-(1{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-2-yl}N-methyl-amino)-acetic acid,
LC/MS (m/z) 384.1 (MH^+); RT = 2.16; purity (UV, ELSD): 97%, 100%; yield: 3.7mg

1ct (S)-(2-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,

LC/MS (m/z) 350.1 (MH^+); RT = 1.97; purity (UV, ELSD): 91%, 97%; yield: 5.5mg

1cu ({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 430.2 (MH^+); RT = 2.73; purity (UV, ELSD): 83%, 100%; yield: 1.0mg

1cv (S)-({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-methyl-amino)-acetic acid,

LC/MS (m/z) 400.0 (MH^+); RT = 2.27; purity (UV, ELSD): 100%, 98%; yield: 3.5mg

1cw ({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl)-N-methyl-amino)-acetic acid,

LC/MS (m/z) 412.0 (MH^+); RT = 2.35; purity (UV, ELSD): 87%, 97%; yield: 3.0mg

1cx ({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-propan-2-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 402.2 (MH^+); RT = 2.53; purity (UV, ELSD): 90%, 99%; yield: 3.4mg

1cy ({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-ethyl-amino)-acetic acid,

LC/MS (m/z) 398.1 (MH^+); RT = 2.24; purity (UV, ELSD): 86%, 96%; yield: 2.3mg

1cz ({2-[2-(4-methoxy-phenylsulfanyl)-phenoxy]-propan-1-yl}- N-Cyclohexyl -amino)-acetic acid,

LC/MS (m/z) 430.3 (MH^+); RT = 2.32; purity (UV, ELSD): 83%, 80%; yield: 1.5mg

1da { [2-(2-(4-methylsulfanyl-phenoxy)-propan-1-yl-]-N-cyclohexyl-amino}-acetic acid,

LC/MS (m/z) 414.4 (MH^+); RT = 2.50; purity (UV, ELSD): 79%, 100%; yield: 1.1mg

1db ({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-cyclohexyl-amino)-acetic acid,

LC/MS (m/z) 434.9 (MH^+); RT = 2.50; purity (UV, ELSD): 98%, 84%; yield: 2.1mg

Example 2

(S)-1-{3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propyl}-pyrrolidine-2-carboxylic acid

1-(3-Iodo-propyl)-2-(3-fluro-phenylsulfanyl)-benzene (48 mg, 0.13 mmol) was dissolved in DMF (0.4 mL). S-Pyrrolidine-2-carboxylic acid *tert*-butyl ester (22 mg, 0.13 mmol) and diisopropylethylamine (25 µL, 0.14 mmol) were added. The mixture was stirred at 50°C for 6 h and then at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in HCl/AcOH (3.1 mL) and stirred overnight. The solvent was removed *in vacuo*. The crude product was purified by preparative LC-MS.

LC/MS (m/z) 360.3 (MH^+); RT = 2.18; purity (UV, ELSD): 89%, 100%; yield: 16.2mg, 34%

Example 3

3a *(S)-1-{2-[4-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid*

A solution of 4-Chloro-2-(3-fluoro-phenylsulfanyl)-phenol (290 mg, 1.14 mmol), PPh_3 (398 mg, 1.52 mmol) in dry THF (6 mL) was cooled to 0 °C. DEAD (0.25 mL, 1.59 mmol) was added dropwise and the solution was stirred for 20 min. A solution of 1-(2-hydroxy-ethyl)-pyrrolidine-2-(*S*)-carboxylic acid *tert* butyl ester (370 mg, 1.72 mmol) in THF (4 mL) was added via canulation. The mixture was stirred for 40 min at 0 °C then for 1.5 h at room temperature and finally for 3 h at 50 °C. The mixture was diluted with heptanes (100 mL), washed with water (4x 25 mL), dried over Na_2SO_4 and evaporated onto silica gel. After flash chromatography using silica gel, eluting with heptanes/EtOAc, 9:1, the intermediate tert butyl ester was obtained as a colorless oil (393 mg, 76%). To a solution of the ester (380 mg, 0.84 mmol) in glacial

HOAc (10 mL) was added HCl in HOAc (1M, 10 mL). The mixture was stirred at room temperature overnight. The solution was evaporated to dryness to give the title compound as a colourless foam Yield: 367 mg, 100%. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.01 (br, 2H), 2.19 (br, 1H), 2.44 (br, 1H), 3.21 (br, 1H), 3.57 (br, 1H), 3.94 (br, 2H), 4.42 (br, 2H), 4.67 (br, 1H), 6.92-7.00 (m, 3H), 7.03-7.06 (m, 1H), 7.11 (br, 1H), 7.21-7.25 (m, 1H), 7.28-7.33 (m, 1H). LC-MS (m/z) 396.0 (MH^+); RT = 2.31; purity (UV, ELSD): 97.1%, 97.9%.

The following compounds were prepared in an analogous fashion:

3b *(S)-1-{2-[3-Chloro-2-(3-fluoro-phenylsulfunyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid*

^{1}H NMR ($CDCl_3$, 500 MHz) 1.86-1.94 (br, 2H), 2.18 (br, 1H), 2.34 (br, 1H), 3.11 (br, 1H), 3.50 (br, 1H), 3.74 (br, 1H), 3.89 (br, 1H), 4.39 (br, 2H), 4.65 (br, 1H), 6.67 (d, 1H), 6.76-6.79 (m, 2H), 6.98-7.00 (m, 1H), 7.18-7.21 (m, 2H), 7.33-7.36 (m, 1H). LC-MS (m/z) 396.1 (MH^+); RT = 2.21; purity (UV, ELSD): 95.1%, 98.7%.;yield 452mg

3c *(S)-1-{2-[5-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid*

^{1}H NMR ($CDCl_3$, 500 MHz) 2.01 (br, 2H), 2.21 (br, 1H), 2.41 (br, 1H), 3.19 (br, 1H), 3.57 (br, 1H), 3.90 (br, 1H), 4.41 (br, 2H), 4.65 (br, 2H), 6.92-6.96 (m, 3H), 7.01-7.06 (m, 2H), 7.14-7.29 (m, 2H). LC-MS (m/z) 396.1 (MH^+); RT = 2.28; purity (UV, ELSD): 93.7%, 99.9%;yield 539 mg

Example 4

4a *(S)-1-[2-(5-Chloro-2-phenylsulfanyl-phenoxy)-ethyl]pyrrolidine-2-carboxylic acid*

A dry round bottomed flask was charged with 1-[2-(5-Chloro-2-iodo-phenoxy)-ethyl]-pyrrolidine-2-(S)-carboxylic acid tert-butyl ester (301 mg, 0.666 mmol), toluene (4.5 mL), KO^{t}Bu (100 mg, 0.89 mmol), thiophenol (78 mg, 0.708 mmol). The mixture was

evacuated and backfilled with argon three times. A separate dry round-bottomed flask was charged with Pd_2dba_3 (9.6 mg, 0.010 mmol) and DPEPhos (16 mg, 0.030 mmol), evacuated and backfilled with argon three times. Toluene (1.5 mL) was added and the mixture stirred at room temperature for 10 min. 1.0 mL of the catalyst mixture was added to the reaction mixture via syringe, and the reaction mixture was heated to 90 °C for 3 h. The mixture was diluted with heptane (6 mL), filtered and adsorbed onto silica gel. After purification by flash chromatography using silica gel, eluting with heptane/EtOAc, 92:8, the tert-butyl ester was obtained as a yellow oil (209 mg, 72%). To a solution of the tert-butyl ester (200 mg) in glacial HOAc (10 mL) was added HCl in HOAc (1M, 10 mL). The mixture was stirred at room temperature overnight. The solution was evaporated to dryness to give the title compound as a colorless foam. Yield: 136 mg, 54%

^{1}H NMR (500 MHz, $CDCl_3$) 2.05 (br, 2H), 2.27 (br, 1H), 2.45 (br, 1H), 3.24 (br, 1H), 3.58 (br, 1H), 3.95 (br, 2H), 4.43 (br, 2H), 4.66 (br, 1H), 6.85-7.00 (m, 2H), 7.13 (br, 1H), 7.26-7.38 (m, 5H). LC-MS (m/z) 377.9 (MH^+); RT = 2.20 min; purity (UV, ELSD): 99.9%, 96.4%;yield 136mg

Pharmacological testing

The compounds of the invention were tested in a well-recognised and reliable test measuring glycine uptake:

[^{3}H]-Glycine uptake

Cells transfected with the human GlyT-1b were seeded in 96 well plates. Prior to the experiment the cells were washed twice in HBS (10 mM Hepes-tris (pH 7,4), 2,5 mM KCl, 1 mM $CaCl_2$, 2,5 mM $MgSO_4$,) and pre-incubated with test compound for 6 minutes. Afterwards, 10 nM ^{3}H-glycine was added to each well and the incubation was continued for 15 minutes. The cells were washed twice in HBS. Scintillation fluid was added and the Plates were counted on a Trilux (Wallac) scintillation counter.

The test results showed, that the prepared compounds of the invention all showed inhibition below 10000 nM as IC_{50} in the above-mentioned assay.

The compounds of the invention were also tested in a well-recognised and reliable microdialysis test.

Method

Male Sprague-Dawley rats, initially weighing 275 - 350 g, were used. The animals were housed under a 12-hr light/dark cycle under controlled conditions for regular in-door temperature (21±2°C) and humidity (55±5%) with food and tap water available *ad libitum*.

Rats were anaesthetized with hypnorm/dormicum (2ml/kg) and intracerebral guide cannulas (CMA/12) were stereotaxically implanted into the brain positioning the dialysis probe tip in the ventral hippocampus (co-ordinates 5.6 mm posterior to bregma, lateral -5.0 mm, 7.0 mm ventral to dura). The rats were allowed to recover from surgery for at least 2 days. On the day of the experiment, a microdialysis probe (CMA/12, 0.5 mm diameter, 3 mm length) was inserted through the guide cannula. The probes were connected via a dual channel swivel to a microinjection pump. Perfusion of the microdialysis probe with filtered Ringer solution (145 mM NaCl, 3 mM KCl, 1 mM $MgCl_2$, 1.2 mM $CaCl_2$) was begun shortly before insertion of the probe into the brain and continued for the duration of the experiment at a constant flow of 1 µl/min. After 165 min of stabilization, the experiments were initiated. A 20 or 40 min sampling regime was used throughout the experimental period. Time points were corrected for lag time of the perfusate from the microdialysis site to the probe outlet.

After the experiments, the rats were sacrificed by decapitation. The brains were removed, frozen and sectioned (20 µm), and the position of the probes was verified.

Analysis of glycine in the dialysates

The concentration of glycine in the dialysates was analyzed by means of HPLC with fluorescence detection after precolumn online derivatisation with o-phatalaldehyde. The system consisted of a Hypersil AA-ODS column (5 µm, 2.1 x 200 mm, Agilent) with a Agilent 1100 fluoresence detector (excitation, 266-340 nm; emission, 305-340 nm). Mobile phases consisted of A: 20 mM sodium acetate, 0.018% triethylamine, 0.3

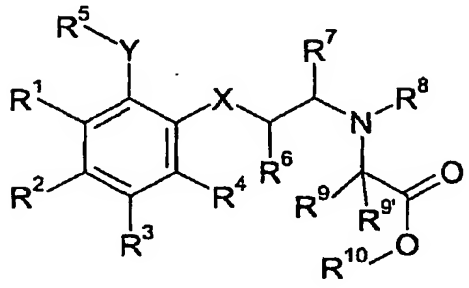
% tetrahydrofuran, pH 7.2. B: 20 mM sodium acetate, 40% acetonitrile and 40% methanol, pH 7.2. The oven temperature was set at 40°C and flow rate was 0.45 ml/min. Data were collected and analysed using ChemStation software (Agilent) after calibration with a range of standard glycine solutions (0.1 –10 µM).

Data presentation

The mean value of 3 consecutive glycine samples immediately preceding compound administration served as the basal level for each experiment and data were converted to percentage of basal (mean basal pre-injection values normalized to 100%).

Claims:

1. A compound of the general formula I



wherein

X is O, S or $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl;

Y is O or S;

R^1, R^2, R^3 and R^4 are independently selected from hydrogen; halogen; cyano; nitro; C_{1-6}-alk(en/yn)yl; C_{1-6}-alk(en/yn)yloxy; C_{1-6}-alk(en/yn)ylsulfanyl; hydroxy; hydroxy-C_{1-6}-alk(en/yn)yl; halo-C_{1-6}-alk(en/yn)yl; halo-C_{1-6}-alk(en/yn)yloxy; C_{3-8}-cycloalk(en)yl; C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; acyl; C_{1-6}-alk(en/yn)yloxycarbonyl; C_{1-6}-alk(en/yn)ylsulfonyl; aryl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl; monocyclic heteroaryl optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl or C_{1-6}-alk(en/yn)ylsulfonyl; or $-NR^{13}R^{14}$ wherein R^{13} and R^{14} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^{13}

and R^{14} together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S or N;

R^5 is aryl or monocyclic heteroaryl, optionally substituted with a halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl, C_{1-6}-alk(en/yn)ylsulfonyl or $-NR^{15}R^{16}$ wherein R^{15} and R^{16} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^{15} and R^{16} together with the nitrogen form a 3-7-membered heterocyclic ring which optionally contains one further heteroatom selected from O, S or N;

R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy, or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl;

R^7 and R^8 are independently selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl; or

R^6 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl; or

R^7 and R^8 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^9 and $R^{9'}$ are independently

selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl; or

R^8 and R^9 together with the nitrogen form a saturated 3-7 membered heterocyclic ring, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and $R^{9'}$ is selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

R^{10} is H, C_{1-6}-alk(en/yn)yl, aryl, aryl-C_{1-6}-alk(en/yn)yl, wherein aryl is optionally substituted with a halogen, CF_3, OCF_3, CN, NO_2 or C_{1-6}-alk(en/yn)yl; or an alkali metal;

or a salt thereof, such as a pharmaceutically acceptable salt.

2. The compound of claim 1 wherein X is selected from O or CH_2.

3. The compound of any one of claims 1-2 wherein Y is O.

4. The compound of any one of claims 1-2 wherein Y is S.

5. The compound of any one of the preceding claims wherein R^1 is selected from hydrogen, C_{1-6}-alkyl, halogen, phenyl, or phenyl substituted with one or two subtituents selected from C_{1-6}-alkyl or C_{1-6}-alkoxy.

6. The compound of any one of the preceeding claims wherein R^2 is selected from hydrogen, C_{1-6}-alkyl, halogen, phenyl or phenyl substituted with one or two subtituents selected from C_{1-6}-alkyl or C_{1-6}-alkoxy.

7. The compound of any one of the preceeding claims wherein R^3 is selected from hydrogen, C_{1-6}-alkyl, halogen, phenyl or phenyl substituted with one or two subtituents selected from C_{1-6}-alkyl or C_{1-6}-alkoxy.

8. The compound of any one of the preceeding claims wherein R^4 is selected from hydrogen, C_{1-6}-alkyl, halogen, phenyl or phenyl substituted with one or two subtituents selected from C_{1-6}-alkyl or C_{1-6}-alkoxy.

9. The compound of any one of the preceeding claims wherein R^5 is phenyl, optionally substituted with a halogen, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl.

10. The compound of any one of the preceeding claims wherein R^6 is selected from H or C_{1-6}-alkyl.

11. The compound of any one of the preceeding claims wherein R^7 is selected from H or C_{1-6}-alkyl.

12. The compound of any one of the preceding claims wherein R^8 is selected from H, C_{1-6}-alkyl or C_{3-8}-cycloalkyl.

13. The compound of any one of the preceding claims wherein R^9 and $R^{9'}$ are independently selected from H or C_{1-6}-alkyl.

14. The compound of any one of the preceding claims wherein R^{10} is H.

15. The compound of any one of claims 1-9 or 14 wherein R^6 and R^8 together with the nitrogen form a 1-pyrrolidinyl, 1-piperidinyl or 1-azepinyl, optionally substituted with a C_{1-6}-alkyl, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl.

16. The compound of any one of claims 1-9 or 14 wherein R^7 and R^8 together with the nitrogen form a 1-pyrrolidinyl, 1-piperidinyl or 1-azepinyl, optionally substituted with a C_{1-6}-alkyl, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^9 and $R^{9'}$ are independently selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl.

17. The compound of any one of claims 1-9 or 14 wherein R^8 and R^9 together with the nitrogen form a 1-pyrrolidinyl, 1-piperidinyl or 1-azepinyl, optionally substituted with a C_{1-6}-alkyl, and R^6 is selected from H, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl or C_{3-8}-cycloalk(en)yl, provided that when R^6 is selected from C_{1-6}-alk(en/yn)yloxy or C_{1-6}-alk(en/yn)ylsulfanyl then X is $CR^{11}R^{12}$, wherein R^{11} and R^{12} independently are selected from H or C_{1-6} alkyl, and R^7 is selected from H, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl, and $R^{9'}$ is selected from H, C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6} alk(en/yn)ylsulfanyl-C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl.

18. The compound of claim 1 selected from
(S)-1-{2-[2-(4-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
(S)- 1-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-{2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,
(S)-1-{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2(S)-carboxylic acid,
(S)-1-{2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(3-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(4-Chloro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(4-Methoxy-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[2-(3,4-Difluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

1-{2(R/S)-[2-(4-Chloro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

1-{2(R/S)-[2-(3,4-Difluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

(S)-1-{2-[2-(3-Fluoro-phenoxy)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

1-{2(R/S)-[2-(3-Fluoro-phenoxy)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

1-{2(R/S)-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

1-{2(R/S)-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propyl}-pyrrolidine-2(S)-carboxylic acid,

({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

2-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N--methyl-amino)-acetic acid,

({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,

{2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,

({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,

{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,

(N-2-propyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,

({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

(N-Ethyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,

2-{3-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

(S)-{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,

({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

(N-2-propyl-{2-[2-(4-methylsulfanyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,

{3-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-ethyl}-N-ethyl-amino)-acetic acid,

({2-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-ethyl-}N-methyl-amino)-acetic acid,

{4-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-piperidin-1-yl}-acetic acid,

2-{3-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-2-propyl-amino)-acetic acid

({2-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,

{2-[2-(4-Methylsulfanyl-phenylsulfanyl)-phenoxymethyl]-piperidin-1-yl}-acetic acid,

({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-ethyl}-N-methyl-amino)-acetic acid,

(N-Methyl-{2-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-ethyl}-amino)-acetic acid,

2-{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

2-{3(R)-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

2-[3(R)-(2-(4-methylphenyl)-sulfanyl-phenoxy)-pyrrolidin-1-yl]-propionic acid,

{3(R)-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-acetic acid,

2-{3(R)-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

2-{3(R)-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-pyrrolidin-1-yl}-propionic acid,

({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,

({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy)-butan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-butan-3-methyl-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[1-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-4-methyl-2-yl)}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]propan-2-yl}-N-ethyl-amino)-acetic acid,

(S)-{1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl }-N-methyl-amino)-acetic acid,

(S)-({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl)-N-ethyl-amino)-acetic acid,

({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(4-Chloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-methyl-amino)-acetic acid,

({1-[2-(4-Chloro-phenylsulfanyl)-phenoxymethyl]-propyl}-N-ethyl-amino)-acetic acid,

(N-Ethyl-{1-[2-(3-fluoro-phenylsulfanyl)-phenoxymethyl]-propyl}-amino)-acetic acid,

(R)-({2-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-1-methyl-ethyl}-N-ethyl-amino)-acetic acid,

(S)-(2{2-[2-(4-Chloro-phenoxy)-phenoxy]-propyl-N-methyl-amino)-acetic acid,

(R)-(2{2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-}-propyl-N-methyl-amino)-acetic acid,

({2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-methyl-amino)-acetic acid,

({3-methyl-1-[2-(4-trifluoromethyl-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-ethyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-butan-2-yl}-N-methyl-amino)-acetic acid,

(S)-(1{2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-2-yl}N-methyl-amino)-acetic acid,

(S)-(2-{2-[2-(3-Fluoro-phenylsulfanyl)-phenoxy]-propyl}-N-methyl-amino)-acetic acid,

({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl}-N-ethyl-amino)-acetic acid,

(S)-({1-[2-(3,4-Dichloro-phenylsulfanyl)-phenoxy]-propan-2-yl}-N-methyl-amino)-acetic acid,

({1-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-3-methyl-butan-2-yl)-N-methyl-amino)-acetic acid,

({1-[2-(4-tert-Butyl-phenylsulfanyl)-phenoxy]-3-methyl-propan-2-yl}-N-ethyl-amino)-acetic acid,

({2-[2-(3-Chloro-4-fluoro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-ethyl-amino)-acetic acid,

({2-[2-(4-methoxy-phenylsulfanyl)-phenoxy]-propan-1-yl}- N-Cyclohexyl -amino)-acetic acid,

{ [2-(2-(4-methylsulfanyl-phenoxy)-propan-1-yl-]-N-cyclohexyl-amino}-acetic acid,

({2-[2-(3-Chloro-phenylsulfanyl)-phenoxy]-propan-1-yl}-N-cyclohexyl-amino)-acetic acid,

(S)-1-{3-[2-(3-Fluoro-phenylsulfanyl)-phenyl]-propyl}-pyrrolidine-2-carboxylic acid

(S)-1-{2-[4-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}-pyrrolidine-2-carboxylic acid,

(S)-1-{2-[3-Chloro-2-(3-fluoro-phenylsulfunyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid,

(S)-1-{2-[5-Chloro-2-(3-fluoro-phenylsulfanyl)-phenoxy]-ethyl}pyrrolidine-2-carboxylic acid,

(S)-1-[2-(5-Chloro-2-phenylsulfanyl-phenoxy)-ethyl]pyrrolidine-2-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound according to any one of claims 1-18 and a pharmaceutically acceptable carrier or diluent.

20. The use of a compound according to any one of claims 1-18 for the preparation of a medicament for the treatment of post-traumatic stress disorder or a disease selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's

disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus.

21. A method for the treatment of a disease or disorder selected from the group consisting of post-traumatic stress disorder, the positive and the negative symptoms of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-18.